Notification and support for people exposed to the risk of Creutzfeldt-Jakob disease (CJD) through medical treatment (iatrogenically) (Protocol)

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*Notification and support for people exposed to the risk of Creutzfeldt-Jakob disease (CJD) through medical treatment (iatrogenically) (Protocol)*

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[Intervention Protocol]

Notification and support for people exposed to the risk of Creutzfeldt-Jakob disease (CJD) through medical treatment (iatrogenically)

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the effects of interventions to notify and support consumers (patients and their carers or families) in situations where exposure to the risk of CJD or vCJD has occurred as a result of medical treatment (iatrogenically), on consumer, carer, healthcare provider and healthcare system outcomes.
BACKGROUND

This review will evaluate the effects of interventions to notify and support consumers exposed to the risk of Creutzfeldt-Jakob disease (CJD) through medical treatment. We plan this review with the awareness that it may not identify any relevant studies for inclusion. However, that interventions for notification and support should be identified, described, categorised, evaluated and this data assembled for summary, is an important aim and one facilitated by the preparation and updating of Cochrane reviews. It cannot be assumed, for instance, that all interventions for these purposes are equally beneficial in terms of their effects.

The aim of this Background section is to describe in depth the population of people ‘at risk’ at the centre of this review. Becoming a person ‘at risk’ arises from several complex and overlapping treatment circumstances, yet the population shares sufficiently similar experiences to be considered together as a group. The background information also aims to describe the ethical issues implicated in interventions targeting this at risk population, and to outline the complexities that must be taken into account in providing interventions to notify and support people at CJD risk, and the evaluation of such interventions.

Creutzfeldt-Jakob disease and other human prion diseases

CJD is a rare and always fatal disease that is not able to be screened for nor treated effectively (NINDS 2008). CJD is the most common of the transmissible spongiform encephalopathies (TSEs), or prion diseases, affecting humans (NINDS 2008; NPC 2008a), and is unusual in that it may be both heritable and transmissible (DHA 2007; NPC 2008a; NPC 2008b; Will 2003). The cause of prion diseases is not yet clearly understood, but is thought to be associated with changes to the prion protein. This protein exists normally within the brain, but can also occur as an abnormally-folded form. The abnormal form of the prion protein is thought to be able to cause other normally-occurring prion proteins to similarly change shape. This leads to further abnormal forms of the prion protein, which aggregate (form clumps). It is thought that this protein accumulation and deposition within the brain leads to progressive and irreversible neuronal damage (Knight 2006; NINDS 2008; NPC 2008a; Pedro-Cuesta 2006; Watts 2006; Ward 2008).

CJD is extremely rare, and a high degree of uncertainty remains about its aetiology, diagnosis and clinical course (CJD IP 2005; CJD SU 2002; NINDS 2008). CJD has an incubation period of variable length before symptoms emerge, but for some acquired forms this may be as long as several decades after a person’s exposure to the infectious prion agent (Brown 2006; NPC 2008a; Will 2003). Once the symptoms of CJD appear, however, the disease progresses rapidly and around 70% of people die within one year of symptoms first emerging (CJD Foundation 2008; NINDS 2008; NPC 2008a). CJD causes brain damage, leading to a range of symptoms which may include profound cognitive changes and dementia, behavioural changes, movement abnormalities and other neurological symptoms such as seizures and visual problems (Appleby 2007; Barnett 2005; CJD SGN 2008; CJD SN 2007). These symptoms are progressive, severe and disabling (Du Val 1997; Pollock 2007; Turner 2003).

At present there is no test to accurately diagnose CJD before the onset of clinical symptoms, and a definitive diagnosis of CJD can be confirmed only by post-mortem examination (Knight 2006; NINDS 2008; vCJD CGAG 2007). Doctors typically make a clinical diagnosis by excluding other neurological or psychiatric diseases that share common symptoms with CJD (Barnett 2005; vCJD CGAG 2007). However, as CJD causes a range of symptoms with varying intensity, and not all patients show all symptoms, or show them in the same sequence, this can cause obvious problems, such as long delays in reaching a diagnosis. This can in turn delay the appropriate medical, health and social services for consumers (patients and their families and carers) (Barnett 2005; Cegelka 2002; Douglas 1999; vCJD CGAG 2007). There may also be delays to the services and support needed by health professionals involved in the patient’s care; for example, the need for accurate, up-to-date information on CJD; or for professional support through access to experts and specialists, in order to best manage their patient’s care (Barnett 2005; vCJD CGAG 2007). These experiences suggest that communication with people affected in some way by CJD is not a one-off event but has implications over time.

How and why do people develop prion diseases?

Currently, there are many uncertainties about prion diseases, and research into diagnosis, prevention, treatment and cure are high priorities (NINDS 2008; Sutton 2006; vCJD CGAG 2007). The prion diseases include a number of different conditions of different aetiology, but can be divided into the following major types (Knight 2006; NINDS 2008; NPC 2008a; Will 2003):

- **Sporadic CJD** accounts for the majority (approximately 80 to 85%) of human TSE cases, although it remains a rare disease in the general population with an incidence of approximately one case per million per year (HPA 2008; NICE 2006; NINDS 2008; NPC 2008a; Pedro-Cuesta 2006). It is not yet clear how or why people spontaneously develop sporadic CJD (Knight 2006).

- **Genetic (inherited) TSEs** are rare and include genetic CJD, as well as Fatal Familial Insomnia (FFI) and Gerstmann Straussler Scheinker syndrome (GSS) (NICE 2006; NINDS 2008; NPC 2008a). A number of specific genetic mutations in the prion protein gene are now known to be associated with the inherited prion diseases (Knight 2006; NPC 2008a; Pocchiari 2004), and different mutations seem to influence the frequency with which the disease appears within families, as well as determining which symptoms are most dominant (NINDS 2008). Genetic screening and predictive prenatal testing are now available for genetic CJD (CJD Foundation 2008; Pedro-Cuesta 2006).

- **Acquired TSEs** are caused by exposure to the infectious prion protein, and include (i) iatrogenic (medically-acquired) CJD and (ii) variant CJD (vCJD, previously called new-variant CJD, nvCJD) (NPC 2008a; Pedro-Cuesta 2006), as now discussed.

(i) **Iatrogenic CJD:** Exposure to prions can occur accidentally through health care. To date, CJD has been acquired through the following medical procedures:

- the use of contaminated batches of intramuscular human pituitary hormones (hPH), including human growth hormones (hGH) and human pituitary gonadotrophins (hPG). People thus exposed form the largest group to date of those exposed to the risk of CJD through medical treatments (NPC 2008b). In these cases, some people were treated with batches of hormones that were produced using organs (pituitary glands) of deceased people who themselves had CJD, or were incubating CJD (were not yet showing...
Medically-acquired (iatrogenic) CJD and vCJD

Internationally, medically-acquired CJD makes up only a very small proportion (less than 1%) of deaths due to CJD (Ladogana 2005; NINDS 2008; NPC 2008b; Ward 2008), and deaths associated with the transmission of CJD via human pituitary hormones and dura mater grafts are declining (Brown 2006). However, as there is no way to screen for either CJD or vCJD, issues of infection control and transmissibility through healthcare routes (such as surgery, blood or tissue donations, or other possible routes) are of major ongoing public health concern (Brown 2006; NICE 2006; Pocchiari 2004; Ponte 2006; vCJD CGAG 2007; Ward 2008). There is concern that people have, and will continue to be exposed to, CJD and vCJD through a range of healthcare procedures. These people form the focus of this review: those at risk of CJD or vCJD acquired through medical procedures, together with their families, carers and healthcare professionals.

The clinical course of medically-acquired CJD varies, and is affected by several factors (Pocchiari 2004), including the dose of the infectious prion to which an individual is exposed through treatment. Genetic factors also play a role: the presence of particular polymorphisms (variations) on the prion protein gene affect an individual’s susceptibility to, or the incubation period of, iatrogenic CJD (NICE 2006; NPC 2008b; Pocchiari 2004; Will 2003) and may even influence the symptoms that people experience (Knight 2006).

The route of CJD transmission, described as central or peripheral, also seems to play a role in the disease's clinical course (Will 2003). People with CJD acquired via intracerebral (central) procedures, such as neurosurgery, tend to show a relatively short incubation period (approximately 18 months to 4 years, but may be as long as 15 years). In contrast, those exposed to CJD via peripheral treatment (that outside the central nervous system), such as via intramuscular injection of contaminated hGH, typically experience longer latent periods (approximately 4 to 25 years, with an average of 12 years) before symptoms develop (Furtner 2008; Llewellyn 2004; NPC 2008a; NPC 2008b; Will 2003). In general, peripherally-acquired CJD has a longer incubation period, prolonged illness and early symptoms of coordination and balance problems when compared with centrally-acquired CJD, which tends to have a shorter latency, progresses rapidly, and in which memory problems and other cognitive symptoms predominate (NPC 2008a; NPC 2008b).

The symptoms of vCJD are different again. For example, people with vCJD tend to experience more prolonged total disease duration than those with sporadic CJD, and initial symptoms are often predominantly psychiatric, such as depression and anxiety (Appleby 2007; CJD Foundation 2006; NPC 2008b; Will 2003). People with vCJD also tend to be younger, with most under 30 years of age (Knight 2006; NPC 2008b). It is not yet clear how long the vCJD incubation period is when people are exposed via diet, although some estimates suggest it may be as long as 10 to 30 years after exposure (CJD IP 2005). Among recipients who appear to have developed vCJD as a result of blood transfusion, the incubation period seems shorter (approximately 6.5 to 8 years), although it may vary between individuals (Hewitt 2006a; Hewitt 2006b; Llewellyn 2004). That the incubation period of vCJD appears to be a matter of several years - whether acquired from diet or secondarily via blood products - is significant: protection of the public health must take account of people potentially incubating the disease as

Notification and support for people exposed to the risk of Creutzfeldt-Jakob disease (CJD) through medical treatment (iatrogenically)

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a result of either exposure, and passing this on to others via blood products in healthcare settings.

Internationally, there is wide variation in the number and geographic distribution of people at risk of CJD and vCJD. For example, compared with other countries, France has a high proportion of iatrogenic CJD cases, which are decreasing over time; whereas the UK shows the highest proportion of vCJD cases which is growing over time (Pedro-Cuesta 2006). Different emerging patterns of CJD and vCJD will dictate who needs to be informed of their exposure to risk, and notification policies will need to be aligned with the latest evidence on CJD and vCJD. The recent confirmation of vCJD transmission through blood, for example, has led to large numbers of individuals being notified of their elevated risk for vCJD above background levels (Dolan 2006; Hewitt 2004; Hewitt 2006a; Hewitt 2006b; Llewelyn 2004). This includes people with haemophilia, who have, as a group, significant experience with iatrogenic risks associated with blood transfusion. Other people notified includes those with no personal prior experience of iatrogenic risks or infections (Hewitt 2006a; Hewitt 2006b). Notification and support processes for iatrogenic CJD and vCJD risk communication must be able to accommodate the experiences and needs of people at both ends of this spectrum, yet the best ways of doing this are not known.

Ethics and notification: public health and individual issues

Regardless of the route of healthcare exposure, CJD and vCJD are serious diseases and there is considerable debate as to the ethical implications of notifying people about exposure to the risk of a fatal disease that is unable to be screened for and about which so much medical uncertainty exists (Barnett 2005; Blajchman 2004; Hewitt 2004; Hewitt 2006a; Steinberg 2001). Guidance in these situations might be informed by the evidence on communicating bad news to patients and their families or carers, and on consumers' expressed preferences in similar situations. Recent studies on communicating bad news to oncology patients and their family members, for example, suggest that communication must take account of the personal impact of the information, and that it must be a planned encounter involving two-way communication between doctors and their patients, as well as between family members or carers (Eggle 2006; Parker 2001). Such encounters must provide information that is comprehensive and understandable, provide support for decision making, and be responsive to the needs of patients and their family members or carers (Eggle 2006). There is less evidence on the best ways to communicate prognostic information for cancer patients, or on the needs and preferences of oncology patients and their families in these situations over time (Hagerty 2005; Parker 2001). Possible guidance in situations where people have been exposed to the risk of CJD or vCJD through medical treatment could also be informed by similar experiences with other healthcare-acquired diseases. For example, worldwide, several incidents have occurred in which people were infected with serious diseases such as Human Immunodeficiency Virus (HIV) or Hepatitis C (HCV) through medical procedures (Bowker 2004; HPA 2008; Myers 2003; Wilson 2007; Worthington 2002). In the last two decades, large numbers of people have been potentially exposed to these diseases through blood transfusion. This led to large recalls of potentially contaminated blood and notification of the individuals involved, in order that people could choose whether to be screened, and then access medical and other support services if, or when, needed (Cagle 2007; Heddle 1997; King 1998; Langley 2001; Wilson 2007).

The high degree of uncertainty associated with medically-acquired risk of CJD and vCJD may, however, distinguish these situations from others involving communication of bad news to patients and families or carers. No effective screening or treatment options yet exist for people at risk of CJD or vCJD; and there is uncertainty about the meaning of the acquired risk for possible future disease. Such uncertainties may make the case for non-disclosure of possible CJD or vCJD exposure stronger than for a disease that has been diagnosed, such as in the case of communicating a diagnosis of cancer; or for healthcare-acquired diseases such as HIV or HCV, for which screening and increasingly effective treatment options exist (Howe 2001; Steinberg 2001).

However, notification of people around iatrogenic incidents is in line with recent moves to support services to disclose openly to patients and their families the facts about adverse incidents that occur when receiving medical care (Iedema 2008; Mazor 2004). There is also a need to protect the public health and to prevent people at risk of CJD or vCJD from donating blood or undergoing healthcare procedures without appropriate infection control measures in place where required (DHA 2007). The balance between precautionary public health priorities versus the individual's rights and the potential harms of notification of CJD or vCJD exposure therefore remains contentious (Bird 2004; DHS 2005; Hewitt 2006b; NINDS 2008; Ponte 2006; Wilson 2004).

What are the options for notifying and supporting people following exposure to the risk of CJD or vCJD through medical treatment?

The consequences of being notified of iatrogenic exposure to the risk of a serious disease such as CJD or vCJD may be profound for the consumers and healthcare professionals involved, and for the health systems in which such incidents occur (DHA 2006; Dolan 2006; Steinberg 2001; Turner 2003; vCJD CGAG 2007). Notification of exposure to the risk of a life-threatening disease, whether the individual goes on to develop the disease or not, has the potential to cause significant distress, anxiety and lasting psychological harm (Duncan 2005; Larke 1998; vCJD CGAG 2007). People notified of exposure to CJD or vCJD risk may also face additional difficulties, such as discrimination or trouble accessing appropriate health or medical care, including restricted access to invasive procedures such as surgery, or to health care such as dentistry (CJD SGN 2008; DHS 2006; Howe 2001; Steinberg 2001; vCJD CGAG 2007).

Ways to ensure the best possible clinical care and support for people exposed to the risk of CJD or vCJD through medical treatment are therefore essential (vCJD CGAG 2007). ‘Lookback’ programmes identify people who have been exposed to a potential source of infection (e.g. recipients of blood potentially contaminated with HIV), notify them of their exposure, and offer the opportunity for testing if this is available. Evaluations of lookback programmes used to notify people of potential exposure to HIV, HCV or CJD have suggested that people are generally positive about receiving such notification. A high proportion of people notified via lookback activities, for example, undergo testing for HIV or HCV following notification (Heddle 1997; King 1997); and notification may enable people to access counselling, therapeutic interventions and additional support services (Heddle 1997; Larke 1998; Younossi 1998). Research also suggests that recipients, in

Notification and support for people exposed to the risk of Creutzfeldt-Jakob disease (CJD) through medical treatment (iatrogenically) (Protocol)
Notification and support for people exposed to the risk of Creutzfeldt-Jakob disease (CJD) through medical treatment (iatrogenically) and referral to specialists, counselling, and provision of detailed accessing specialist telephone help lines, follow-up appointments and supported over time. These include strategies such as vCJD, there are different ways in which they might be followed-assembled and evaluated.

The impact of notification

Relatively little is known about the effects of notification of exposure to CJD or vCJD risk on psychological, emotional and social outcomes for consumers. Research indicates that several factors, including the individual's personality, may influence the impact of notification (Langley 2001; Sibbald 1998). This suggests that the effects of notification may differ markedly between individuals (Hewitt 2004; Larke 1998), and even for those who are most certain they wish to be notified of disease risk exposure there may be harms associated with notification, and ongoing support may be needed (Larke 1998). However, the range of impacts on people notified of exposure to CJD or vCJD risk is not well documented, and there is little information to identify: those who might be adversely affected, or most at risk of harms arising from notification; what types of harms might arise; and how to prevent or minimise potential harms associated with notification. Given that a range of responses to notification of the risk of iatrogenic CJD/vCJD exposure may exist, there may not be a single best way to notify all people in these situations (Farrugia 2005; Sibbald 1998).

Notification of at-risk status

If people are to be notified of the risk of iatrogenic exposure to CJD or vCJD, how should it be carried out and by whom (Larke 1998)? There are many different ways in which people might be notified of their exposure to risk. This includes: conveying the information using a range of different formats (e.g. consultation with healthcare provider, letter, telephone call); providing the information through different people or organisations (e.g. treating physician, specialist, health service); presenting the risk information on CJD/ vCJD in different ways (e.g. as an absolute risk versus relative risk, as a natural frequency, as a lifetime probability); and using a range of delivery features (such as varying the timing of the notification, or different components of the notification strategy, providing training to those involved in communicating with people at risk, and establishing notification processes ahead of time) (Callum 1999; DHS 2006; Farrugia 2005; Freedman 1997; Hewitt 2006a; Hewitt 2006b; King 1998; Reesink 2003; vCJD CGAG 2007). The notification strategy may also incorporate more than one component and/or format. There are potentially, therefore, many different approaches to notification. The evidence on what people need or would prefer in these situations, however, has yet to be systematically assembled and evaluated.

Support and follow-up post-notification

Once people have been notified of their at-risk status for CJD or vCJD, there are different ways in which they might be followed-up and supported over time. These include strategies such as accessing specialist telephone help lines, follow-up appointments and referral to specialists, counselling, and provision of detailed information on CJD and vCJD (DHS 2006; Freedman 1997; Hewitt 2006a; Hewitt 2006b; King 1998; Reesink 2003; vCJD CGAG 2007). Again, approaches might incorporate more than one component. The necessity of living with the uncertainties of risk and prognosis once notified, possibly over many years, may significantly impact people’s ongoing psychological, emotional and physical wellbeing (Meek 1998; Steinberg 2001). An international forum of experts recently recommended that extensive follow-up and referral to specialists be provided routinely to people notified of exposure to CJD (Reesink 2003). However, the needs of people at risk immediately following the notification, and over time, are not well documented. As a result, the best ways of meeting their needs are unknown.

The long latency of CJD and vCJD suggests that the responses and needs of people at risk may change over the person's lifetime. It is also likely that, in time, some of the uncertainties of CJD and vCJD risk, and the meaning of this risk for future disease, are likely to become clearer. A recent report highlighted, for example, that as the uncertainties around CJD/ vCJD start to be resolved, or if a sensitive and specific test becomes available, the people involved will need to be informed and supported appropriately at each stage (vCJD CGAG 2007). As knowledge about CJD and vCJD grows, there will therefore need to be strategies in place to appropriately convey this information to patients and their families, as well as to healthcare professionals.

Relationship to other relevant reviews

The scope of this review covers a wide range of interventions, such as information provision, education, notification and disclosure, counselling and supportive care. These interventions are likely to overlap with those of existing Cochrane and non-Cochrane systematic reviews. However, the focus of this review on medically-acquired CJD/ vCJD is narrow and we have not identified any reviews which focus on these situations or populations.

Several Cochrane reviews and protocols are relevant to the scope of this review. One particularly relevant review is 'Methods of communicating a primary diagnosis of breast cancer to patients' (Lockhart 2007), which found no studies for inclusion. Other Cochrane and non-Cochrane reviews we have identified, such as those dealing with communication in serious diseases, and breaking bad news, have been used to inform our choice of outcomes, and we will discuss the findings of the current review in the context of these related reviews (such as Davies 2003, Leliopoulos 2001, NICE 2004 and Walsh 1998).

Why this review is important

Little is known about the best ways to notify people of potential exposure to the risk of CJD or vCJD through medical treatment, what people need or would like, or how best to support them during and after the notification.

In this review we focus solely on people at risk of CJD or vCJD following potential iatrogenic exposure. The rationale for this is the high degree of uncertainty around the diagnosis, transmission, treatment and clinical course of CJD and vCJD, which set them apart in important ways from other serious, medically-acquired diseases. As the body of knowledge on CJD and vCJD grows, and informs practice and policy, this accumulated knowledge will need to be communicated accurately and sensitively to consumers. In the interim there are individuals, families and groups facing the
uncertainty of CJD and vCJD risk, and the best ways of notifying these people and supporting them in the face of what is known about the disease has yet to be systematically assembled and evaluated. Effective ways to inform and support people at risk in relation to infection control measures are also needed over time, to promote both people's capacity to manage their health care, as well as to promote healthcare responses that are appropriate to the person's individual risk level.

Poor practices in the past mean that these issues remain important. For instance, although the widespread therapeutic use of cadaver-derived hPH ceased over two decades ago, the long latency of CJD means that cases may continue to emerge amongst this population (Brown 2006; Furtner 2008; Pedro-Cuesta 2006). In addition, those cases arising spontaneously, those associated with heritable disease, and cases of vCJD will continue to emerge and the people affected will invariably have contact with healthcare systems (Knight 2006; Will 2003). Even if effective screening and treatment options become available, it may not be possible to identify all people with emerging CJD or vCJD as they have contact with healthcare systems. This means that people will continue to be exposed to these risks iatrogenically. Effective ways to notify people of potential risk in these circumstances, to support them and to best organise their care should they develop CJD or vCJD will therefore remain a high priority into the foreseeable future.

We have planned this review with the awareness that it may be an 'empty Cochrane systematic review', that is, a review without included studies to form the basis of analysis, synthesis and conclusions (Green 2007; Lang 2007). We believe that, nevertheless, the review will: identify interest in the process of good communication with people at risk of iatrogenic CJD or vCJD; highlight research gaps; contribute to the systematic identification of the range of interventions and outcomes that could form the basis of rigorous studies in this area; and provide a status report of research that will be regularly updated (Lang 2007). Furthermore, this review has been commissioned by the Public Health Division of the Department of Human Services Victoria, Australia, which has concurrently commissioned us to conduct a separate review of the evidence, irrespective of study design, relevant to consumers' and carers' experiences of being notified of being at risk of CJD or vCJD as a result of medical procedures. We intend to provide an accessible link in this Cochrane protocol and subsequent review to the other 'non-Cochrane' literature review, and we will discuss its findings and their implications in this review. We present methods for doing so in the Data collection and analysis section ('Relation to non-Cochrane literature review' heading).

As more is known about the aetiology and treatment of CJD and vCJD, we will revise the scope of this review to fit the changing evidence base. As for policy and practice, it will be important to keep this review regularly updated to reflect new evidence (vCJD CGAG 2007). Although the importance of strategies for notifying and supporting people in relation to iatrogenic exposure to CJD and vCJD risk is well recognised, the best ways of doing so are not known. These strategies are the focus of this review.

**OBJECTIVES**

To evaluate the effects of interventions to notify and support consumers (patients and their carers or families) in situations where exposure to the risk of CJD or vCJD has occurred as a result of medical treatment (iatrogenically), on consumer, carer, healthcare provider and healthcare system outcomes.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We will include all randomised (individual and cluster), quasi-randomised and non-randomised controlled studies (controlled before and after studies (CBAs) and interrupted time series (ITS) analyses).

Although non-randomised studies may be more prone to bias, randomised controlled trials (RCTs) may not always be possible or practical. For example, it is unlikely that many RCTs will have been conducted in situations where people must be promptly notified of potential exposure to a serious disease. CJD and vCJD are also rare diseases; and there is not yet clear consensus on whether it is more ethically sound to inform people, or not to inform them, of their risk of exposure. These factors also suggest that few controlled studies will exist to assess the interventions that form the focus of this review.

Given the importance of this topic and the need to evaluate the best available evidence, we will include other study designs (quasi-RCTs, CBA and ITS). To be eligible for inclusion, CBA and ITS studies must each meet two quality criteria outlined in the Cochrane Consumers and Communication Review Group guidelines (Ryan 2007).

**Types of participants**

We will include people of any age, gender or ethnicity at risk of CJD or vCJD acquired via medical treatment (whether or not they are also genetically predisposed to CJD and other prion diseases); their families and/or carers, and/or the healthcare professional(s) involved in their care.

The risk of CJD or vCJD can be associated with any medical or surgical treatment, and includes those people at secondary risk of vCJD through blood transfusion.

We will exclude:

- People for whom the risk of CJD or vCJD was not acquired through medical treatment, including:
  - * People exposed to the risk of vCJD through diet (BSE-contaminated meat consumption).
  - * People and families for whom the risk for CJD or other prion disease is solely genetic in origin. The rationale for this exclusion is that families in which genetic CJD risk exists may choose to undergo genetic screening to identify this risk. This process involves a range of different communication issues to those where an individual's risk of CJD is acquired iatrogenically. We aim to complete a separate review focusing on communication and support interventions for people with a genetic CJD risk and their families and carers in the future.
- People with probable or confirmed CJD or vCJD and their families and carers. The rationale for this exclusion is that people dealing with an actual disease, rather than the possibility of exposure to the risk of disease, have a distinct range of needs and experiences, and face a different range of issues and decisions, to those of people at risk. We aim to complete...
a further review on communication and support interventions focusing on people with CJD or vCJD and their families and carers in the future.

Types of interventions

Any intervention aiming to notify or support people who have been exposed to the risk of CJD or vCJD through medical treatment. In this review, we use the term 'notify or support' broadly to mean all interventions to communicate with and notify, educate, inform, seek the participation of and support people in these situations.

For people at risk and their families/carers, examples include interventions to:

- Notify or inform people of their exposure to the risk of CJD or vCJD - e.g. letter, telephone call, consultation with GP or other healthcare professional.
- Inform or educate people about the disease risk to which they may have been exposed - e.g. information about the disease or risk of disease and the current state of knowledge and uncertainty about prion diseases; the risk of transmission and/or precautionary measures that must be taken to protect the public health (e.g. when receiving medical or other health treatment; when considering blood, tissue or organ donation).
- Support people following notification - e.g. supportive counselling or family-based interventions.
- Improve the continuity of care or provide follow-up for people notified of the risk of CJD or vCJD, or the healthcare professionals involved in the notification process and/or the provision of care, including interventions in time periods immediately following notification, as well as at later time points.

Interventions can be delivered in any setting (e.g. hospital, home, community); via any format or medium (e.g. letter, telephone, face-to-face consultation); and by any provider (e.g. clinician, community health worker, peers or family).

The intervention may have one or several components. It may be delivered solely to the patient (person at risk), and/or to their families or carers; and may be delivered to individuals or to groups or families.

Interventions may also be delivered to healthcare professionals involved in notifying and/or supporting consumers, but only where the intervention aims specifically to equip the professional with the skills and resources to communicate more effectively. In such cases the study must report at least one consumer-oriented outcome to be eligible for inclusion.

We will include the following comparisons:

- Interventions to notify or support people versus no intervention.
- Interventions to notify or support people versus standard or usual care.
- One form of intervention to notify or support people versus another - including simple versus complex interventions.

We will exclude:

- Interventions aiming to notify people or support them in relation to genetic risk of CJD or other prion disease.
- Interventions communicating with or support patients or their families and carers in relation to a probable or confirmed diagnosis of CJD/vCJD.

Studies will be organised into broad categories according to the major aims of the intervention; for example, those aiming to notify people of exposure to the risk of CJD or vCJD; those aiming to provide information or education in relation to CJD/vCJD; and those aiming to support people following notification of exposure to the risk of CJD or vCJD.

We will also consider the nature and quality of the intervention as an organising principle. For example, where possible, we will separate simple interventions from those that are complex (vCJD CGAG 2007); and we will consider the training and support for those delivering the interventions (e.g. interventions where the provider is specifically trained and/or supported to deliver the intervention, versus those where there is no training and/or support) (Herbert 2005). We will also consider process evaluations and whether these indicate that the intervention as delivered was of high quality.

Types of outcome measures

A range of outcomes relevant to consumers, to healthcare providers and to healthcare systems may be affected by interventions to notify and support consumers following iatrogenic exposure to the risk of CJD or vCJD. There will be no exclusions based on the outcomes reported by studies that are otherwise eligible for inclusion in this review, other than where the intervention targets healthcare professionals (where at least one consumer-oriented outcome must be reported).

We will seek data on the following outcomes (for a more detailed list of outcomes to be sought see Appendix 1):

Consumer-oriented outcomes, including:

- Knowledge and understanding, e.g. understanding of how the risk was acquired, perceived risk.
- Communication, e.g. satisfaction with communication.
- Patient involvement in care, e.g. involvement in decision-making.
- Evaluation of care, e.g. satisfaction with care or interventions received.
- Support, e.g. whether people used practical or psychosocial support (such as information, counselling), and the effects of support (such as perceived or actual support, social function, isolation).
- Skills acquisition, e.g. self-care skills.
- Health status and wellbeing, e.g. physical or psychological health outcomes.
- Health behavior, e.g. attitudes towards a disease or health care.
- Treatment outcomes, e.g. clinical outcomes.

The term consumer-oriented outcomes is used here to refer to patients and to their families and/or carers.

We will also seek data on potential harms and adverse events associated with the interventions, for the patient, family members and/or carers, and for the healthcare providers involved in delivering interventions or care and management. This will include emotional and psychological harms, such as anxiety, psychological...
distress and fear. We will also consider harms relating to changes in access to medical and health treatments, and perceived and actual discrimination, and we will identify any complaints regarding services or personnel.

**Healthcare provider-oriented outcomes, including:**

- Knowledge and understanding, e.g. levels of knowledge about CJD/vCJD and prognosis, infection control.
- Consultation processes, e.g. level of patient-centred care.
- Support, e.g. support and/or training received in notifying patients.
- Health service use, e.g. provider behaviour such as appropriate referral.
- Health status and wellbeing, e.g. psychological health outcomes for the provider.

**Health service delivery-oriented outcomes, including:**

- Service delivery level, e.g. use of care plans or teams; communication between care teams.
- Societal or governmental, e.g. healthcare policy/legislation/procedures and revisions of these.

Given the long latency of CJD and related diseases, we will evaluate and report information on outcomes in both the short term (e.g. immediately following intervention delivery) and at all longer-term time points for which data are available.

**Search methods for identification of studies**

**Electronic searches**

We will search the following electronic databases:

- Cochrane Consumers and Communication Review Group Specialised Register
- Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library);
- MEDLINE (OVID SP);
- EMBASE (OVID SP);
- PsycINFO (OVID SP);
- CINAHL (EBSCO Host);
- Current Contents (OVID SP) (Social & Behavioural Sciences, Clinical Medicine);
- Dissertation Abstracts (Proquest); and
- Sociological Abstracts (CSA).

We will search all databases from their start date to the present. The search strategy for MEDLINE is presented in Appendix 2. Strategies will be tailored to other databases and full details of the searches will be reported in the review. There will be no language or date restrictions. Nor will there be search filters or restrictions based on study design.

As part of the study selection process, we will screen citations retrieved from database searches for studies that otherwise fit the review scope but do not meet the study design inclusion criteria (e.g. qualitative research, process evaluations, consensus documents, surveys). These studies will be summarised systematically, and their findings synthesised and reported thematically. This will form the basis of a separate but complementary (non-Cochrane) review that will synthesise the findings of qualitative and other relevant research. Major findings of this broad review will be included in an appendix to this review, and used to inform the organisation and interpretation of results and discussion.

**Searching other resources**

We will search grey literature, including relevant government, health agency and consumer websites.

We will contact experts in the field and authors of included studies for advice on other relevant studies. We will not handsearch journals but will search reference lists of relevant studies and reviews; and will cross-check relevant papers and authors using ISI Web of Science and PubMed (related articles function) to locate additional relevant materials.

**Data collection and analysis**

**Selection of studies**

Two authors working independently will screen the titles and abstracts of studies identified from the search for inclusion. We will retrieve in full text any papers identified as relevant by at least one author.

Two review authors will independently screen full text articles for inclusion or exclusion, with discrepancies resolved by discussion and by consulting a third author if necessary. All papers excluded from the review at this stage will be listed as excluded studies, with reasons provided in the Characteristics of excluded studies table. We will also provide citation details and any available information about ongoing studies.

**Data extraction and management**

Two review authors will independently extract data from all included studies, with any discrepancies resolved by discussion and consensus, or through consultation with a third author where necessary.

We will develop and pilot a data extraction form using the Cochrane Consumers and Communication Review Group Data Extraction Template (available at: www.latrobe.edu.au/cochrane/resource.html). Further details of the data to be extracted from included studies is given in Additional Table 1.

All extracted data will be entered into RevMan by one review author, and will be checked for accuracy against the data extraction sheets by a second review author working independently.

**Assessment of risk of bias in included studies**

Two review authors will independently assess the risk of bias of each included study, with disagreements resolved by discussion and consensus, and by consulting a third review author if necessary. Studies of different designs will be dealt with separately throughout this review in both the quality assessment and analysis.

For RCTs (and quasi-RCTs), we will assess and report on the following elements that contribute to bias, according to the guidelines outlined in Higgins 2008:

- sequence generation;
- allocation concealment;
• binding of participants, personnel and outcome assessors;
• incomplete outcome data; and
• selective outcome reporting.

We will describe the study and assign a judgement relating to the risk of bias for each item, following the guidance in Higgins 2008. We will rate each item as ‘yes’ (indicating a low risk of bias), ‘no’ (a high risk of bias), and ‘unclear’ (risk of bias is unclear). For each study we will summarise the risk of bias for each outcome.

We will also assess a range of other possible sources of bias and indicators of study quality, in accordance with the guidelines of the Cochrane Consumers and Communication Review Group (Ryan 2007), including:

• baseline comparability of groups;
• validation of outcome assessment tools;
• reliability of outcome measures;
• other possible sources of bias (e.g. contamination or co-intervention).

If studies other than RCTs and quasi-RCTs (CBA and ITS studies) are included in the review, we will also assess the risk of bias and quality of these studies. We will adapt the risk of bias criteria for these study designs, based on guidance in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008) and that of the Cochrane Consumers and Communication Review Group (Ryan 2007); and will describe the study and assign a judgement relating to the risk of bias for each item.

We will incorporate the results of the risk of bias and quality assessment into the review through systematic narrative description and commentary about each of the assessed items, for each type of included study. This will lead to an overall assessment of the risk of bias across the included studies and a judgement about the possible effects of bias on the effect sizes of the included studies.

We will attempt to contact authors of included studies for additional information about the included studies, or for clarification of the study methods, as required.

Measure of intervention effects
Where quantitative data are available, we will extract means and variances, numbers of participants on which results are based, and results of any tests of statistical significance. Where possible we will use RevMan to report quantitative data. For individual RCTs, quasi-RCTs and CBA studies we will calculate relative risks (RR) and 95% confidence intervals (CI) for dichotomous data. For continuous data where outcome scales are similar, we will calculate the mean difference (MD) and 95% CI. Where outcome scales are variable we will calculate the standardised mean difference (SMD) and 95% CI. For ITS studies, we will calculate the mean difference in outcomes before and after intervention delivery.

Unit of analysis issues
If cluster-randomised controlled trials are included, we will check for unit of analysis errors. If required and sufficient data are available we will recalculate the results using the appropriate unit of analysis (Higgins 2008).

Dealing with missing data
Where data are missing, we will attempt to contact authors of included studies to obtain complete data. Where possible, we will conduct analysis on an intention-to-treat (ITT) basis; otherwise data will be analysed as reported. We will report on the levels of loss to follow-up and assess this as a source of potential bias.

Assessment of heterogeneity
We anticipate that a substantial degree of heterogeneity will exist due to differences in the interventions and outcome measures, study designs and the methodological quality of included studies. Although the scope of this review is narrow in terms of the disease risks considered eligible, we also expect that there may be variation in the populations included, such as whether people at risk have been exposed to a confirmed or theoretical risk of CJD or vCJD, or the age of the people involved. There will also be variation between people based on risk level. For example, there are people at a higher risk level as a result of exposure through human pituitary growth hormone treatment, or haemophiliacs exposed through blood transfusion, when compared with neurosurgical routes of exposure which are considered to confer a lower risk.

We will therefore consider systematically any differences in populations, interventions and outcomes in the synthesis of data to determine whether statistical pooling of results is appropriate and likely to yield meaningful results.

Where studies are considered similar enough clinically to consider pooling data, we will assess the degree of heterogeneity by visual inspection of forest plots and by examining the I² statistic (Higgins 2008).

Assessment of reporting biases
We will examine funnel plots for asymmetry to check for possible publication bias (Higgins 2008).

Data synthesis
We will conduct a narrative synthesis of results. We will present the major outcomes and results, organised by intervention categories according to the major types and/or aims of the identified interventions, such as: interventions to notify people of risk; to inform or educate; to support people following notification or diagnosis; to improve continuity of care or follow-up; and to improve self-care or self-management. Depending on the assembled research, we may explore the possibility of organising the data by population (e.g. people ‘at risk’ of CJD or vCJD; people ‘at theoretical risk’ of CJD; healthcare providers involved in notifying and/or supporting people at risk); or by setting (e.g. home, hospital). The decision on which way to categorise and organise the data will also be informed by the accompanying non-Cochrane literature review.

Within the data categories we will group results by study type. Within each data category, the main comparisons will be:

• Intervention versus no intervention.
• Intervention versus standard or usual care.
• One form of intervention versus another.

Notification and support for people exposed to the risk of Creutzfeldt-Jakob disease (CJD) through medical treatment (iatrogenically) (Protocol)
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Where studies compare more than one intervention, we will compare each separately to no intervention/ control; and with one another.

In the case of limited data being included in this review, we will also provide a description of which notification and support strategies have been tested, what their key components were, their content, format and other relevant features. This description will also be informed by the accompanying non-Cochrane literature review.

We will explore possible reasons for variability in findings in the systematic narrative analysis. Exploration of potential effect modifiers may include investigating characteristics of the interventions; variations in the populations assessed (e.g., CJD risk, vCJD risk, theoretical CJD risk, the age of the individuals involved); the different risk levels associated with the route of exposure (e.g. neurosurgical routes, blood transfusion, hormone treatment); the timing of notification relative to the treatment through which exposure to risk occurred; or the influence of different settings upon the effects of the interventions examined. Exploration of potential effect modifiers in the narrative analysis will be performed with the aim of informing the development of best practice recommendations based on the available evidence.

Where studies are sufficiently similar in terms of populations, inclusion criteria, interventions and/or outcomes, we will consider pooling the data statistically. We will use a fixed-effects model unless substantial heterogeneity is detected. If substantial heterogeneity is detected, either through visual inspection or by an elevated I² statistic, then a random-effects model will be used. We will conduct separate meta-analysis, where appropriate, to pool the results of studies within major intervention types (e.g. interventions to notify, educate, support) and within each included study type (RCT, quasi RCT, CBA, ITS).

We will analyse and present the findings for each major intervention type organised by the outcomes: consumer-, provider- and system-oriented outcomes respectively. Adverse effects and harms will be analysed and presented separately.

**Subgroup analysis and investigation of heterogeneity**

We do not anticipate identifying enough studies to justify statistical subgroup analyses to explore underlying causes of variability in the findings. Although we have not planned subgroup analysis, this review may help to identify potential subgroup analyses for investigation in future versions of the review; for example, considering different sub-populations of people at risk (e.g. CJD risk, vCJD risk, theoretical CJD risk; the age of those involved); or considering different risk levels associated with routes of exposure (e.g. neurosurgical routes, blood transfusion, hormone treatment).

**Sensitivity analysis**

If adequate data are available, we will conduct sensitivity analyses to investigate the effects of study quality. We will investigate study quality as a possible source of heterogeneity by comparing the results of studies of lower methodological quality with those of higher relative methodological quality.

**Relation to non-Cochrane literature review**

As outlined, we are concurrently conducting a separate broad literature review (Ryan 2008). The central question of this second review is: what are the best ways to notify and support consumers in situations where exposure to the risk of CJD (or vCJD) has occurred as a result of medical treatment? This literature review includes studies of diverse methods that identify consumers’ and carers’ views and experiences of being notified of their at-risk status for CJD or vCJD, and their needs with respect to notification and support. Drawing from the evidence reviewed, and from consensus views, key themes were identified and used to organise and analyse the data. These themes were also used to develop a model for a comprehensive, multi-component framework for improving notification, communication with, and support for people in relation to CJD or vCJD risk acquired medically. The model has informed the identification of the range of possible interventions and outcomes outlined in this protocol.

We will systematically relate the findings of this broad literature review to those of the current review. For example, data from the broad review may be used to interpret the findings on intervention effectiveness by systematically considering people’s views and preferences for such interventions; to assess the effectiveness of interventions in the light of people’s identified needs in relation to notification and support interventions; or to consider the possible harms arising from the use of identified interventions.

**Consumer involvement**

For each included study, we will collect information about the involvement and role of consumers in the development and evaluation of the interventions.

The protocol has been reviewed by consumer referees, as per standard Review Group editorial processes, to ensure the applicability and acceptability of the review to consumers and to ensure that consumers’ views are represented appropriately. The process will be repeated at the review stage.

**Acknowledgements**

We are grateful to the staff and editors of the Cochrane Consumers and Communication Review Group, particularly to Nancy Santesso, Shirley Ward and John Kis-Rigo for assistance in developing and refining search strategies; to Sandy Oliver for invaluable advice as contact editor for this protocol; to Megan Pritchard (Review Group Coordinator); and to external peer referees (including content experts and consumers) for their helpful feedback. We also thank Cathy Mead and Michael Taylor, other members of the project team from the Australian Institute for Primary Care, and the members of the Victorian Department of Human Services Reference Group, for feedback and assistance in developing the scope of this review.

We have been assisted immeasurably by a number of experts across the fields of CJD and prion diseases, and/or transmissible diseases associated with medical treatment. These experts provided advice and information which assisted us to develop the scope of this review. We are also very grateful to Suzanne Solvyns (Director, CJD Support Group Network, Australia) for her involvement, assistance with obtaining relevant materials and in making contact with experts and others. We also gratefully acknowledge the helpful feedback from referees for this protocol.
### References

**Additional references**

- **Allars 1994**

- **Appleby 2004**

- **Barnett 2005**

- **Bird 2004**

- **Blajchman 2004**

- **Bowker 2004**

- **Brown 2006**

- **Cagel 2007**

- **Callum 1999**

- **Caulfield 1997**

- **Cegelka 2002**
  Cegelka J. Creutzfeldt-Jakob disease: the psychological effect it has on caregivers. PhD thesis. The Union Institute and University Graduate College. 2002. [UMI 3061988]

- **CJD Foundation 2008**

- **CJD IP 2005**

- **CJD SN 2007**

- **CJD SU 2002**

- **Davies 2003**

- **DHA 2007**

- **DHS 2006**

- **Dolan 2006**
Notification and support for people exposed to the risk of Creutzfeldt-Jakob disease (CJD) through medical treatment (iatrogenically)

**Douglas 1999**

**Du Val 1997**

**Duncan 2005**

**Eggy 2006**

**Farrugia 2005**

**Freedman 1997**

**Furtner 2008**

**Green 2007**

**Hagerty 2005**

**Hart 2004**

**Hedde 1997**

**Herbert 2005**

**Hewitt 2004**

**Hewitt 2006a**

**Hewitt 2006b**

**Higgins 2008**

**Howe 2001**

**HPA 2008**

**Iedema 2008**

**King 1995**

**King 1997**

**King 1998**

**Knight 2006**
Ladogana 2005

Lang 2007

Langley 2001

Larke 1998

Leliopoulo 2001

Llewelyn 2004

Lockhart 2007

Mazor 2004

Meek 1998

Myers 2003

NICE 2004

NICE 2006

NINDS 2008

NPC 2008a

NPC 2008b

Parker 2001

Pedro-Cuesta 2006

Pocchiari 2004

Pollock 2007

Ponte 2006

Reesink 2003

Ricketts 1997
### Table 1. Planned data extraction

<table>
<thead>
<tr>
<th>Data to be extracted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY DETAILS</strong> - including:</td>
</tr>
<tr>
<td>• Authors and year of publication.</td>
</tr>
<tr>
<td>• Details of the study - including aims, recruitment, selection criteria, ethics approval, funding sources and consumer involvement.</td>
</tr>
<tr>
<td>• Country and setting.</td>
</tr>
<tr>
<td>• Time span of the trial.</td>
</tr>
<tr>
<td>• Details of analysis performed.</td>
</tr>
<tr>
<td>• Consumer involvement and participation - including their role in developing and evaluating the intervention.</td>
</tr>
</tbody>
</table>

| **PARTICIPANT DETAILS** - including: |
| • Pre-trial calculation of sample size. |
| • Participant characteristics - such as age, gender, ethnicity, diagnosis and details of comorbidities. |
Table 1. Planned data extraction (Continued)
- Participant numbers - recruited, randomised and analysed.

INTERVENTION DETAILS - including:
- Intervention aims.
- Development of the intervention.
- Characteristics of the intervention - such as the medium/format, content, intensity and other delivery features (e.g. individual versus group, setting where delivered, frequency and timing, provider and training/support of the provider), and the different components of the intervention.
- Characteristics of control (usual care) or alternative interventions will also be extracted, as well as co-interventions where applicable.
- Quality and integrity of the intervention.

OUTCOME DETAILS - including:
- Primary outcomes and outcome measures.
- Secondary outcomes and outcome measures.
- Adverse events.
- Method and timing of outcome measurement - for each reported outcome.
- Validity of outcome measures - for each reported outcome.
- Reliability of outcome measures - for each reported outcome.

RISK OF BIAS DETAILS - including rating (yes, no, unclear) and information on each of the following:
- Sequence generation.
- Allocation concealment.
- Blinding of participants, personnel and outcome assessors.
- Incomplete outcome data.
- Selective outcome reporting.

Other study quality indicators:
- Baseline comparability of groups.
- Validity and reliability of outcome assessment tools.
- Other possible sources of bias (such as contamination or co-intervention).

OTHER INFORMATION - including
- Details of author contact and results

APPENDICES

Appendix 1. Detailed outcomes to be assessed
We will collect information on a range of outcomes relevant to consumers (patients and their families/carers), health professionals and health systems. We will seek data on the following outcomes:

Consumer-oriented outcomes, including:
- Knowledge and understanding - e.g. Understanding of how the risk was acquired; understanding of the risk status of the patient and the risk levels (infectivity) associated with different tissues and medical procedures; understanding of the disease, its progression and outcome; knowledge of availability of health and support services; knowledge of treating professionals, eligibility for additional services, such as counselling; perceived risk, accuracy of, or change in accuracy of perceived risk; patient’s or family members’ wishes regarding whether to be informed or not;
- Communication - e.g. use of communication aides; satisfaction with communication;
• Patient involvement in care - e.g. involvement in decision-making; decisional conflict; preferences (e.g., for information, treatments, services or support); patient-held information;
• Evaluation of care - e.g. perceptions/ ratings of care or interventions received; satisfaction with care or interventions or processes or decisions;
• Support - e.g. whether people accepted practical or psychosocial support (such as information, counselling), and the effects of support (such as perceived or actual support, social function, isolation, burden).
• Skills acquisition - e.g. communication skills; self-care skills; caregiving skills;
• Health status and wellbeing - e.g. quality of life; physical or psychological health outcomes for the patient, carer and/or family, including emotional outcomes such as fear, anxiety or distress;
• Health behavior - e.g. attitudes towards a disease or health care; adherence to recommended care or acceptance of health care; risk-taking behaviours; use of services including screening/ diagnostic services; and
• Treatment outcomes - e.g. physiological/ clinical outcomes, follow-up, adverse events including access to medical treatment and health services.

We will also seek data on potential harms and adverse events associated with the interventions, for the patient, family members and/or carers, and for the healthcare providers involved in delivering interventions or care and management. This will include consideration of emotional and psychological harms, such as anxiety, psychological distress and fear. We will also specifically consider harms relating to changes in access to medical and health treatments; and perceived and actual discrimination. We will identify any complaints regarding services or personnel.

Healthcare provider-oriented outcomes, including:
• Knowledge and understanding - e.g. attitudes and behaviours; levels of knowledge (such as, about CJD and prognosis, infection control and transmissability, specialist and other care requirements, patient’s or carer’s wishes);
• Consultation processes - e.g. level of patient-centred care; choices offered in the provision of care;
• Support - e.g. support and/or training received in notifying patients;
• Health service use - e.g. provider behaviour such as active and appropriate referral; co-ordination of care and follow-up; and
• Health status and wellbeing - e.g. physical or psychological health outcomes for the provider.

Health service delivery-oriented outcomes, including:
• Service delivery level - e.g. service use (such as use of specialist care, hospital admissions); coordination and continuity of care; use of care plans and/or teams; communication between sectors and/or care teams or care manager; and
• Societal or governmental - e.g. healthcare policy/legislation/procedures and revisions of these; healthcare monitoring, health care planning, procedural changes; health professional training; quality improvement strategies.

Appendix 2. MEDLINE search strategy
1. exp disclosure/
2. duty to recontact/
3. exp "referral and consultation"/
4. contact tracing/
5. exp Counseling/
6. exp population surveillance/
7. (disclos$ or notif$ or duty to recontact).tw.
8. (privileged communication or bad news).tw.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10.(cjd or jakob$).tw.
11.exp prion diseases/
12.exp dementia/
13.10 or 11 or 12
14.exp Cross Infection/
15.exp Blood Transfusion/
16.(blood adj2 transfusion$).tw.
17.disease outbreaks/
18.exp disease transmission/
19.exp Equipment Contamination/
20.exp Postoperative Complications/
21. exp Surgical Procedures, Operative/
22. (tissue donor$1 or blood donor$1).tw.
23.14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. (prion$ or spongiform$ or encephal$ or blood-borne or dementia or pseudosclerosis or nevin or heidenhain or iatrogenic).tw.
25.23 and 24
26.13 or 25
27.9 and 26
28. humans.sh.
29.27 and 28

CONTRIBUTIONS OF AUTHORS

RR: developed the review scope; searched for papers and contacted experts; and wrote the protocol.
KA: assisted with providing statistical and methodological advice; and contributed to protocol drafts.
SH: initiated the review and developed the scope; and contributed to protocol drafts.
DL: assisted with locating and screening relevant papers; and contributed to protocol drafts.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources
- No sources of support supplied

External sources
- Department of Human Services, Victoria, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)
*Disease Notification; *iatrogenic Disease [epidemiology]; Creutzfeldt-Jakob Syndrome [epidemiology] [*transmission]; Prion Diseases [epidemiology] [transmission]

MeSH check words

Humans